

WO 00/56749

PCT/US00/04032

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N-ACYLPHOSPHORAMIDITES AND THEIR USE IN OLIGONUCLEOTIDE
SYNTHESIS

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12/28/04
THIS APPL. IS A 371 OF PCT/US00/04032 FILED 2/16/00
WHICH CLAIMS BENEFIT OF 60/125867 FILED 3/24/99.
TECHNICAL FIELD OF THE INVENTION

5 The present invention relates to the synthesis of
oligonucleotides, and intermediates useful in the
synthesis thereof.

BACKGROUND OF THE INVENTION

10 Since the development of efficient and reliable
methods for automated synthesis of oligonucleotides, and
early observations about the potential therapeutic
application of oligonucleotides, there is a high demand
for new oligonucleotide analogues. This demand is due to
15 the fact that natural oligonucleotides undergo very rapid
nucleolytic degradation to monomeric nucleosides and
nucleotides in biological fluids *in vitro* and/or *in vivo*.

 The therapeutic application of oligonucleotides is
based on the selective formation of hybrids between
20 antisense oligonucleotides and complementary nucleic
acids, such as messenger RNAs (mRNAs). Such hybrids
inhibit gene expression by blocking protein translation.
Successful inhibition of gene expression, however,
requires the antisense oligonucleotide to be nuclease
25 resistant so that it can be transported through
biological membranes and can hybridize selectively to a
target complementary nucleic acid, thereby actively
blocking protein translation. Among the diverse
oligonucleotide analogues that have been tested for
30 antisense activity, those bearing phosphorothioate
internucleotide linkages are the most nuclease resistant
and, therefore, are the most widely used.